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CASE REPORT

Increased levothyroxine requirements presenting as "inappropriate" TSH secretion syndrome in a patient with nephrotic syndrome

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ABSTRACT. Patients with primary thyroid failure on levothyroxine (LT_4) replacement who develop nephrotic syndrome (NS) may rarely present with an increase in LT_4 requirements. In this report, we describe a patient with thyroid failure following radioactive iodine ablation for Graves' disease who required an escalation of LT_4 doses following the onset of NS. The case presented with disproportionately elevated TSH levels in the presence of normal (or slightly subnormal) thyroid hormone levels, thus, masquerading as a state of "inappropriate" TSH secretion. This pattern of extreme dysregulation in thyroid function indices due to urinary loss of thyroid hormones has not been previously described in NS, and, therefore, extends the spectrum of endocrine manifestations of NS.
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INTRODUCTION

The nephrotic syndrome (NS) is defined as the combination of proteinuria (urinary protein excretion >3.5 g/d), hypoproteinemia, hypercholesterolemia, and peripheral edema, caused by increased permeability of the glomerular capillaries (1). Numerous abnormalities in thyroid function indices have been described in patients with NS, including low serum protein-bound iodine (PBI) (2), low serum thyroxine-binding globulin (TBG) (2, 3), as well as increased urinary excretion of PBI (3, 4), TBG (5), thyroxine (T_4), triiodothyronine (T_3) (6-11), free T_4, free T_3 (12-14), and thyrotropin (TSH) (15). In addition, reverse (r)T_3 metabolism has also been shown to be significantly altered in NS, as patients with heavy proteinuria demonstrate low serum levels of rT_3 and free rT_3 (16). Despite urinary losses of both free and protein-bound thyroid hormones, serum levels of free T_4, free T_3 and TSH remain normal in most patients with NS (4, 12, 16-18). However, non-autoimmune, reversible hypothyroidism may occur in rare cases of NS, manifested by low serum thyroid hormone (TH) levels and/or compensatorily increased serum TSH (6, 7, 10, 14, 19). Elevated serum TSH levels are more frequently encountered in infants than in patients in other age groups with NS (9, 13, 20-24). Most patients that develop significant changes in either TSH or free TH levels remain clinically euthyroid, although those patients with both biochemical abnormalities become myxedematous and require TH replacement therapy (10, 12, 14, 17, 23, 24).

In patients with pre-existing primary thyroid failure who are on levothyroxine (LT_4) replacement, the onset of heavy proteinuria due to NS may rarely lead to increased serum TSH levels, and, hence, an increase in LT_4 requirements to prevent clinically overt hypothyroidism (14, 20, 25). However, the hypothalamic-pituitary-thyroid (HPT) axis feedback

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Key-words: "Inappropriate" TSH secretion, nephrotic syndrome, levothyroxine, hypothyroidism, proteinuria.

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mechanisms in NS have been shown to be intact (14, 16, 20).

We describe herein an athyroid patient on LT_4 replacement who presented with markedly elevated serum TSH levels following the onset of NS, and required large exogenous TH doses for normalization of TSH levels, leading to an ususual presentation reminiscent of a state of "inappropriate" TSH secretion.

CASE REPORT

A 41-yr-old man presented with NS due to membranous nephropathy. The diagnosis was established by a kidney biopsy, showing characteristic light and electron microscopic findings. The patient had no evidence of underlying systemic disease; however, he had a history of Graves' disease treated with radioiodine (131-I) 11 years previously. He was clinically and biochemically euthyroid on LT_4 replacement (average oral [po] daily dose: 162.5 µg, stable over several years). Other medications included atorvastatin, 10 mg po daily, for the management of secondary hypercholesterolemia (due to NS) and a multivitamin preparation (containing no iron supplementation). Two months after the diagnosis of NS, the patient was referred to the National Institutes of Health (NIH) for further management.

Upon his initial presentation at the NIH, the patient denied any symptoms of thyroid dysfunction. Physical examination was remarkable only for moderate pedal edema. There were no signs consistent with extrathyroidal manifestations of Graves' disease, hypo- or hyperthyroidism; no goiter was evident. Blood pressure was 127/86 mmHg, while pulse rate was 77/min. The patient's weight was 72.2 kg at a height of 176 cm (body mass index [BMI]: 23.3). At that point, the patient's thyroid function tests showed a profound elevation of serum TSH levels in the presence of normal free T_4 (Table 1). Furosemide was initiated at a dose of 80 mg po daily, along with metolazone 10 mg po daily, with subsequent improvement of the patient's peripheral edema.

The patient's LT_4 replacement dose was increased to 200 µg daily, and the patient was re-evaluated in 3 months, *i.e.*, 5 months after the initial diagnosis of NS. The patient's thyroid function indices were measured using the following methods: total T_3 and free T_4: competitive electrochemiluminescent immunoassay (ECIA); TSH: two-site "sandwich" ECIA; TBG: solid-phase two-site ECIA; reverse (r)T_3: radioimmunoassay (RIA); and free T_4 by dialysis: dialysis followed by RIA. The free T_4, total T_4, total T_3, and TSH assays were performed on an Elecsys 2010® immunoassay analyzer (Roche Diagnostics, Indianapolis, IN), showing the following operative characteristics: free T_4: analytic sensitivity (AS): 0.023 ng/dl, maximum precision at (P @): 1.64 ng/dl, intra-assay coefficient of variation (Intra-CV): 1.7%, and inter-assay coefficient of variation (Inter-CV): 3.3%; total T_4: AS: 0.23 µg/dl, P @: 9.59 µg/dl, Intra-CV: 2.7%, Inter-CV: 3.7%; total T_3: AS: 19.5 ng/dl, P @: 187 ng/dl, Intra-CV: 4.2%, Inter-CV: 4.7%; and TSH: AS: 0.005 µU/ml, P @: 0.91 µU/ml, Intra-CV: 2.1%, Inter-CV: 3.3% (26-30). TBG assays were performed on an Immulite® immunoassay analyzer (Diagnostic Product Corp., Los Angeles, CA). The rT_3 and free T_4 by dialysis assays were performed on a United Technologies Packard® analyzer, while the free T_3 assay was performed on a Ciba-Corning Diagnostics® ACS:180 system (both assays performed at the Mayo Medical Labs, Rochester, MN), showing the following operative characteristics: free T_4 by dialysis: AS: 0.2 ng/dl, P @: 1.8 ng/dl, Intra-CV: 5.3%, Inter-CV: 7.4% (31); and free T_3: AS: 50 pg/dl, P @: 341 pg/dl, Intra-CV: 2.4%, Inter-CV: 2.6% (32).

By the time of the patient's re-evaluation, his proteinuria had markedly increased, and TSH levels had risen even further, in spite of the LT_4 dose escalation, as well as in the face of a normal free T_4 (Table 1). Notably, serum T_3 and free T_3 levels were only minimally depressed below normal (Table 1), while TBG was 13 µg/ml (normal [nl] range: 12-30 µg/ml), free T_4 by dialysis was 0.8 ng/dl (nl range: 0.8-2.7 ng/dl), and rT_3 was 21 ng/dl (nl range: 25-75 ng/dl). The levels of anti-thyroglobulin and anti-thyroid-peroxidase antibodies were 22 IU/ml (nl range: 0-59 U/ml) and 98 IU/ml (nl range: 0-59 U/ml), respectively. Thyroid-stimulating immunoglobulin (TSIg) levels were elevated at 2.8 Index Units (nl range: 0-1.3 Index Units), as were the levels of TSH-binding inhibitory immunoglobulins (TBII), at 28% inhibition of binding (nl range: 0-9.9% inhibition of binding). The above serologic profile was consistent with the patient's history of Graves' disease. An extended battery of serologic screening tests for generalized autoimmune diseases and viral infections was negative. A Westergren erythrocyte sedimentation rate (ESR) was normal, while serum immunoglobulin electrophoresis showed no paraprotein bands.

The discrepancy between the dramatically elevated serum TSH and normal (or only slightly subnormal) serum TH levels was further investigated. The patient's compliance to all prescribed medications was assessed by direct questioning by both the medical and clinical pharmacology teams during

Table 1 - *Biochemical and clinical parameters during the development and treatment of nephrotic syndrome.*

Parameters	Units	Normal range	Prior to diagnosis of NS: Baseline	Following diagnosis of NS: 2 mos	5 mos	6 mos	7 mos	8 mos	9 mos	13 mos
Proteinuria	g/d	0.03-0.10	NT	3.1	20.7	15.2	NT	NT	9.7	10.8
TSH	μU/ml	0.43-4.60	0.95	55	176	94	95	53	0.42	0.25
Free T_4	ng/dl	0.9-1.6	1.7	1.2	0.9	1.2	1.2	1.6	1.6	1.1
Total T_3	ng/dl	75-170	121	NT	71	70	81	69	256	111
Free T_3	pg/dl	230-420	NT	NT	210	NT	270	270	700	NT
Urinary T_4	μg/dl	0.675-1.475	NT	NT	NT	NT	NT	NT	2.01*	NT
Urinary free T_4	ng/dl	0.081-0.641	NT	NT	NT	NT	NT	NT	1.320	NT
Dose of LT_4 replacement	μg/d	115-140 (average range)	162.5	162.5	200	200	200	225	225	188
	μg/kg/d	1.6-2.0 (average range)	2.53	2.35	2.77	2.69	2.84	3.17	3.26	3.03
Other medications									LT_3 (50 μg/d)	CyA (250 mg/d)
				Atorvastatin, furosemide, M-Vit, metolazone						

*Total 24 h urine volume=2,200 ml; absolute urinary T_4 execretion=44.2 μg/d. CyA=cyclosporine A; d=d; LT_4=levothyroxine, LT_3=liothyronine; mos=months; M-Vit=multivitamin; NS=nephrotic syndrome; NT=not tested.

each visit, as well as by formal pill counts performed by a pharmacist. The possibility that our patient might have been taking additional LT_4 tablets by filling prescriptions in other local pharmacies other than our own was also excluded. Malabsorption of exogenous TH, a very rare phenomenon, was then considered. This could be playing an important role in our case, especially in view of the small bowel edema seen in patients with severe NS (33). Although LT_4 malabsorption would explain the initial failure to achieve adequate levels of free T_4 in the serum, it would fail to justify the fact that serum TSH remained elevated despite adequate levels of free T_4 for several weeks. Further, our patient did not develop other signs of intestinal malabsorption, such as anemia, diarrhea, abdominal bloating or waisting. Additionally, factitious pseudomalabsorption of LT_4 was also excluded, as our patient was truly highly compliant with his medications (34).

We allowed for an interval of at least two weeks after each LT_4 dose change before any testing was performed. Further, the patient did not take more than the daily prescribed amount of LT_4. Thus, we believe that the availability of oral LT_4 was fairly stable at each time point of our evaluation. Notably, the patient also omitted his morning LT_4 dose prior to any TSH measurement; he was taking that LT_4 dose after all blood samples were collected. TSH samples were obtained between 8:00-9:00 h following an overnight fast, in order to avoid interference of these measurements with the TSH diurnal rhythm (35).

With regard to the possibility of drug interactions, although lovastatin and simvastatin have been associated with reduction of LT_4 absorption in some cases (36, 37), no such reports exist for atorvastatin, the lipid-lowering agent our patient was treated with. Further, in our patient, atorvastatin was administered prior to bedtime, while LT_4 was given in the morning, and, hence, the two medications were administered almost 14 h apart. Our patient was also treated with furosemide, a drug that could displace T_4 from transthyretin and TBG, leading to an apparent decrease in serum total T_4, and consequent increase in free T_4 (38). Notably, this effect is usually noticed at high doses of this diuretic (39). However, in our patient we observed either normal or slightly subnormal serum free T_4 values. If furosemide were responsible for an apparent elevation of serum free T_4, this would actually lead to a tendency for the TSH to be subnormal (or at least not markedly elevated), assuming that the patient's HPT axis was normal. Moreover, the patient was on a relatively modest dose of furosemide (80 mg po daily), and never received the parenteral form of the medication. Finally, during the time of our investigation, our patient was not treated with non-steroidal anti-inflammatory drugs, aspirin, or salicylate (either prescribed or "over-the-counter"), medications which are also known to displace T4 from serum protein binding sites (39).

No anti-T_3, anti-T_4 (40), anti-TSH (41), or heterophilic antibodies (42) were detected. Mixing experiments of the patient's serum with pooled sera or TSH standards, according to published methods (42-44), failed to reveal a substance that would interfere with the TSH assay. The LT_4 preparation that the patient was taking was a brand name, and not a generic one. The LT_4 content of the prescribed tablets was determined only for the 200 µg tablets, which would have provided the majority of the prescribed dose (highest LT_4 dose prescribed in this patient: 225 µg po daily). The consistency of the LT_4 content for tablets of different strengths and/or different batches over time was not tested. The 200 µg LT_4 tablets were ground to a fine powder, extracted, and analyzed by high-performance liquid chromatography (HPLC) (45); their LT_4 content was 89% of predicted, which was just below the acceptable threshold for quality control according to the U.S. Pharmacopeia (content of active substance should be no less than 90% of predicted) (45).

The possibility that non-thyroidal illness (NTI) could have significantly affected the values of the thyroid function tests obtained by the assays used herein was also entertained. Although NS can be classified as a NTI, notably our patient was never systemically ill, and all indices of chronic illness and/or inflammation, including an ESR, were absolutely normal. Further, the patient's creatinine clearance (CrCl) ranged between 112 ml/min and 137 ml/min during the time of investigation, and, hence, there was no degree of renal failure associated with the patient's NS at any time point. The effects of NTI upon the serum total T_4, total T_3, free T_4, free T_3, and TSH values measured by the assays we used have not been specifically validated. This is an important consideration, as free T_3 levels have been shown to be highly method-dependent in patients with NTI. This effect was noted by Sapin and colleagues in their detailed study of comparing six different free T_3 assays in patients with NTI (46). However, NTI in this paper was designated as liver cirrhosis and renal failure. Notably, our patient's hepatic function was excellent, and, as noted above, his CrCl remained completely normal even in the face of heavy proteinuria. The free T_4 by dialysis assay we used in this study has been formally validated, and shown not to be significantly affected by the presence of NTI (31).

Finally, variations of TSH bioactivity have been recorded in patients with non-thyroidal illness (47). It is theoretically possible that alterations in TSH bioactivity-over-immunoreactivity (B/I) ratios could have significantly contributed in the observed anomalies in the HPT axis in this case; unfortunately, TSH B/I ratios were not determined serially over time in our patient.

The patient's LT_4 replacement dose was subsequently further increased to 225 µg po daily, and he was re-evaluated in the next 3 months, *i.e.* 8 months after the initial diagnosis of NS. Despite escalation of the LT_4 replacement dose, the serum TSH remained markedly elevated, now in the face of free T_4 levels at the upper limit of the normal range (Table 1). Because of the above biochemical picture, we now consider the syndrome of "inappropriate" TSH secretion.

Thyrotropin-releasing hormone (TRH) stimulation and acute LT_3 suppression tests showed TSH response patterns consistent with primary hypothyroidism (Fig. 1, panels A and B), and not with either

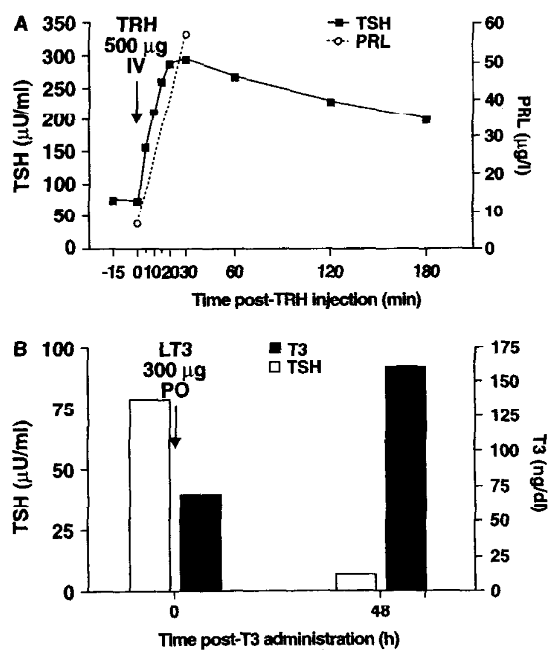

Fig. 1 - *Panel A. Serum TSH and prolactin (PRL) responses to a standard TRH stimulation test (500 µg intravenously [iv] bolus) in our patient. Panel B. Serum TSH and T_3 at baseline and 48 h after the administration of liothyronine (LT_3) (300 µg po bolus) in the context of an acute T_3 suppression test, as described by Nicoloff and colleagues (50). Serum T_3 levels increased significantly following LT_3 administration, while free T4 levels remained unchanged (data not shown). The post-T_3 TSH levels decreased to less than 10% of baseline, thus effectively excluding pathologic causes of "inappropriate" TSH secretion and confirming the integrity of the HPT axis in this case.*

resistance to thyroid hormone or TSH-producing pituitary tumor (48-50). Notably, an acute load of LT_4 was not given to our patient. T_4 has a long half-life, and we doubt that an acute large T_4 load would have made a significant difference in the "steady-state" serum concentrations of free T_4 achieved in our patient. In order to investigate the integrity of the HPT axis in our patient, an acute T_3 load was administered instead, in the context of an acute LT_3 suppression test.

Serum baseline prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocotricotropin (ACTH), and cortisol levels were normal. Serum fasting growth hormone (GH) levels were undetectable, while plasma insulin-like growth factor-1 (IGF-1) levels were within reference limits. The glycoprotein α-subunit (α-SU)/TSH molar ratio was normal, at 0.67 (nl values for normogonadotropic patients in the presence of TSH elevation <0.7 [51]). Pituitary magnetic resonance imaging (MRI) showed a partially empty sella, but no evidence of tumor or hyperplasia. Several indices of peripheral thyroid hormone action (52-54) were measured, and their serum levels were as follows: retinol: 69.7 μg/dl (nl range: 36-120 μg/dl), sex hormone-binding globulin (SHBG): 218 μg/dl (50.5 nmol/l) (nl range: 43-346 μg/dl [10-80 nmol/l]), creatine phosphokinase (CPK): 149 U/l (nl range: 52-386 U/l), ferritin: 91 μg/l (nl range: 10-300 μg/l), osteocalcin: 7 μg/l (nl range: 2-15 μg/l), angiotensin-converting enzyme (ACE): 10.0 U/l (nl range: 36-120 U/l), and apolipoprotein A-I: 149 mg/dl (nl range: 90-203 mg/dl). These indices were within the normal range, thus excluding defects in the TH receptor-dependent signaling mechanisms in peripheral tissues. The dynamic responses of the HPT axis (Fig. 1, panels A and B), as well as the normal state of other pituitary hormones, effectively excluded a pathologic cause of "inappropriate" TSH secretion.

Following the acute LT_3 suppression test, the patient was maintained on LT_4 at a dose of 225 μg po daily, and LT_3 was added to the LT_4 regimen at a dose of 50 μg po daily. On this regimen, the patient's TSH eventually became very minimally suppressed, while he developed symptoms of mild thyrotoxicosis (mainly manifesting occasional palpitations, mild tachycardia, and anxiety). The urinary excretion of T_4 and free T_4 was assayed according to established methods (55, 56), and was found to be moderately elevated (Table 1). Unfortunately, a 24 h urine specimen obtained earlier during the course of the patient's NS was mishandled and never assayed for TH urinary levels. Hence, no comparisons could be made between the single measurement of the level of urinary TH losses at the 9 months time point and those at earlier time points, thus, hampering us from demonstrating excessive and continuous urinary TH losses throughout the patient's course. We assume, however, that massive such losses would have occurred earlier on.

The patient eventually reached "steady-state" with regard to LT_4 metabolism, as serum TSH became normal and the mild thyrotoxic symptoms dissipated. At that point LT_3 was discontinued, and the patient was maintained on LT_4 alone at a dose of 188 μg po daily. He was also started on cyclosporine A (250 mg po daily), and showed marked improvement in the manifestations of his NS.

DISCUSSION

Graves' disease can very rarely be associated with the nephrotic syndrome (NS) in an etiopathogenic basis; causes include thyroid antigen-mediated immune complex glomerulonephritis, propylthiouracil-induced antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis, methimazole-induced direct glomerular toxicity, and IgA nephropathy (57-63). It is notable that our patient's serum contained both anti-thyroglobulin and anti-TSH receptor antibodies, and it is at least theoretically possible that immune complexes of either of the above antibodies with their respective antigens could be involved in the pathogenesis of NS. Since the presence of extractable thyroid antigen-antibody complexes from kidney biopsy specimens was not assessed, a causal relationship between such presence and the development of NS could not be determined in this case. Additionally, the diagnosis of NS in our case followed the development of Graves' disease by several years, and most thyroidal antigens might have been extinct by then, especially in the face of prior radioiodine therapy. Thus, in this case it is likely that the two diseases are coincidental.

Non-autoimmune hypothyroidism has been rarely observed following the onset of NS; this is characterized by low serum TH levels due to massive urinary TH losses, and results in increased serum TSH (6, 7, 10, 14, 19). When such efflux of TH occurs in patients who are on levothyroxine (LT_4), the HPT axis is severely perturbed, as evidenced by the presence of abnormally low free TH levels, elevated TSH levels, and increased LT_4 requirements (14, 20, 25). Under these circumstances, the serum TSH level may reach values as high as 48 μU/ml [Case #4 in (14)]. In all cases described heretofore, a moderate escalation of exogenous LT_4 dose has promptly led to normalization of serum TSH, as well as the reversal of hypothyroid symptoms. However, serum free T_3 levels have been shown to remain significantly depressed in several cases (16, 20). In our case, the increase in exogenous LT_4 requirements was striking and was probably due to increased urinary TH losses, leading to failure of achieving "steady-state" serum TSH levels. Unfortunately, we can only assume that urinary TH losses were persistently high, as we were able to demonstrate increased urinary excretion of T4 and free T_4 only in one 24 h urine collection sample.

The disproportionate increase in TSH in the presence of normal (or slightly subnormal) serum free TH levels masqueraded as "inappropriate" TSH secretion, a biochemical picture that has not been previously reported in association with NS. Moreover, although this pattern of thyroid function indices can be seen transitorily in the recovery phase of NTI, in which case the HPT axis is not in "steady-state" (68), our patient was not severely or acutely ill at any time during his evaluation. Further, he never developed any degree of renal impairement, despite massive proteinuria.

In previous studies, a positive correlation has been demonstrated between the degree of proteinuria and the level of urinary TH and TBG losses (10, 12, 13, 18). Furthermore, the mean serum free T_4 levels in patients with detectable urinary T_4 was reported to be significantly lower than in patients with undetectable urinary T_4 (14). In the same study, the patients with detectable urinary T_4 also presented with the heaviest proteinuria. In our patient, the highest TSH level did indeed coincide with the highest rate of urinary protein excretion [5 months following the diagnosis of NS (Table 1)], in agreement with the above reports. In patients with NS and hypothyroidism, reversal of massive proteinuria by bilateral nephrectomy, prednisone administration, and low protein diet has resulted in reversal of the hypothyroid state (9, 65-67). However, it is not clear whether the excessive urinary T_4 loss reflects merely the severity of the renal lesion *vs* a loss of selectivity of the glomerular membrane leading to excretion of TBG and T_4. In fact, modulation of this glomerular filter selectivity over time may explain the fact that in our case the serum thyroid function indices were dissimilar despite the same degree of proteinuria at different times during the course of NS. Notably, the usually log-linear relationship of serum TSH to free T_4 levels was not constant in our patient during the time of evaluation. We do not believe that this effect was due to artifacts in the biochemical assays of thyroid function used in this study.

With regard to the phenomenon of maintenance of relatively normal serum free T_4 levels in the face of heavy proteinuria [*i.e.* at the time point of 5 months since the diagnosis of NS (Table 1)], we have considered the possibility of the existence of circulating serum "factors" modifying the dissociation of TH from plasma transport proteins, as a compensatory mechanism for such an effect. However, our finding of a low-normal free T_4 by dialysis, a TH quantification method mostly unaffected by serum interfering substances, excludes a mechanism based on modulation of TH binding to plasma proteins by such substances. Similar observations to ours have been made by Kaptein *et al.*, who have shown that the free fraction of T_4 is modestly increased in patients with NS in comparison to normal controls. The mechanism for this effect remains unclear (16), but is not believed to involve redistribution of TH from plasma binding sites.

The extreme degree of TSH elevation observed herein and its apparent "resistance" to suppression by escalating doses of exogenous T_4 has been exhaustively investigated with regard to all possible causes already described in the literature. We conclude that these effects are due to a transitory acquired state of resistance to TH in this particular case. Mechanistically, this apparent resistance could be due to reduced free T_3 availability at the level of the hypothalamus and/or pituitary, and hence "inappropriately" elevated TSH secretion and/or production. Free T_3 levels at these central sites absolutely depend on the abundance of free T_4, as well as on availability of enzymatic action of 5'-deiodinase (68-70). The inability of large doses of exogenous T4 to suppress TSH secretion in our patient was in sharp contrast to the prompt normalization of serum TSH after exogenous LT_3 administration. This may suggest at least a partial deficiency in the amount and/or activity of pituitary 5'-deiodinase. Interestingly, peripheral conversion of T_4 to T_3 was found to be enhanced rather than decreased in rats with NS induced by puromycin aminonucleoside (71), although the function of hypothalamic and/or pituitary 5'-deiodinase was not addressed in that study.

With regard to possible mechanisms leading to reduced availability of free T_3 at the central components of the HPT axis, Benvenga *et al.* reported on the case of a male patient with Perthes' disease, as well as several non-syndromic skeletal abnormalities, who presented with a state of inappropriate TSH secretion, thought to be compatible with pituitary 5'-deiodinase deficiency (72). This patient was clinically euthyroid, and had an empty sella, normal baseline serum α-SU levels, normal responsiveness of TSH to TRH and an acute T_3 load, as well as minimal evidence of peripheral refractoriness to TH. In direct similarity to our patient, the patient described by Benvenga and colleagues also showed persistent inability of high-normal free T_4 levels (up to 1.53 ng/dl) to effectively normalize his serum TSH. Interestingly, however, this patient was proven to have the syndrome of resistance to TH later on [one of three cases reported in (73)]. Thus, although that patient did not have NS, he was the first one in whom a central 5'-deiodination defect has been implicated to explain the biochemical features of his HPT axis. Further studies are warranted to clarify the proposed molecular mechanism of HPT axis dysregulation in NS, *i.e.* hypothalamic and/or pituitary 5'-deiodinase deficiency.

In conclusion, this case expands the spectrum of endocrine manifestations of nephrotic syndrome to include severe HPT axis dysregulation due to a persistent failure to achieve "steady-state" serum TSH levels. This picture can be easily confused with and needs to be differentiated from the syndrome of "inappropriate" TSH secretion.

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